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From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

CAMPBELL & FLORES
Attn. FAN, Calvin A.
4370 La Jolla Village Drive
Suite 700
SAN DIEGO, CALIFORNIA 92122
UNITED STATES OF AMERICA

DOCKETED

IDS) Search Rpt

3-18-01

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

RECEIVED

Date of mailing
(day/month/year)

18/12/2000

Applicant's or agent's file reference

FP-TB4193

JAN 03 2001

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US 00/15310 CAMPBELL & FLORES

International filing date

(day/month/year)

02/06/2000

Applicant

TRIAD THERAPEUTICS, INC.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Jaap Hurenkamp

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 52.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | | |
|---|---|---|--|
| Applicant's or agent's file reference FP-TB4193 | | FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
| International application No. PCT/US 00/15310 | International filing date (day/month/year) 02/06/2000 | (Earliest) Priority Date (day/month/year) 04/06/1999 | |
| Applicant TRIAD THERAPEUTICS, INC. | | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

NMR RAPID IDENTIFICATION OF BI-LIGAND DRUG CANDIDATES

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☒ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

2b

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

Application No

JP/US 00/15310

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/68 G01N33/53 G01N33/542 C12Q1/32

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | S B SHUKER ET AL: "Discovering High-Affinity Ligands for Proteins: SAR by NMR" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE, US, no. 274, 1996, pages 1531-1534, XP002074440 ISSN: 0036-8075 cited in the application the whole document --- -/-- | 1-49, 52 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

17 November 2000

Date of mailing of the international search report

18/12/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Hart-Davis, J

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|---|-----------------------|
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| A | P J HAJDUK, G SHEPPARD ET AL.: "Discovery of Potent Nonpeptide Inhibitors of Stromelysin Using SAR by NMR" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 119, no. 25, 1998, pages 5818-5827, XP002153164 cited in the application the whole document | 1-49,52 |
| A | --- E T OLEJNICZAK, P J HAJDUK ET AL.: "Stromelysin Inhibitors Designed from Weakly Bound Fragments: Effects of Linking and Cooperativity" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 119, no. 25, 1997, pages 5828-5832, XP002153165 the whole document | 1-49,52 |
| A | --- HAJDUK PHILIP J ET AL: "NMR-based discovery of lead inhibitors that block DNA binding of the human papillomavirus E2 protein." JOURNAL OF MEDICINAL CHEMISTRY, vol. 40, no. 20, 1997, pages 3144-3150, XP002153166 ISSN: 0022-2623 the whole document | 1-49,52 |
| A | --- WO 97 18469 A (ABBOTT LAB) 22 May 1997 (1997-05-22) cited in the application the whole document | 1-49,52 |
| A | --- SCAPIN GIOVANNA ET AL: "Three-dimensional structure of Escherichia coli dihydrodipicolinate reductase in complex with NADH and the inhibitor 2,6-pyridinedicarboxylate." BIOCHEMISTRY, vol. 36, no. 49, 9 December 1997 (1997-12-09), pages 15081-15088, XP002153167 ISSN: 0006-2960 cited in the application abstract | 1,6-8, 12,14,15 |
| | --- -/-- | |

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| A | <p>REDDY SREELATHA G ET AL: "Interaction of pyridine nucleotide substrates with Escherichia coli dihydrodipicolinate reductase: Thermodynamic and structural analysis of binary complexes." BIOCHEMISTRY, vol. 35, no. 41, 1996, pages 13294-13302, XP002153168 ISSN: 0006-2960 cited in the application figures 3,5,6</p> | 1,6-8, 12,14,15 |
| A | <p>REDDY SREELATHA G ET AL: "Expression, Purification, and Characterization of Escherichia coli Dihydrodipicolinate Reductase." BIOCHEMISTRY, vol. 34, no. 11, 1995, pages 3492-3501, XP002153169 ISSN: 0006-2960 cited in the application page 3498 -page 3500</p> | 1,6-8, 12,14,15 |
| A | <p>LIN GIALIH ET AL: "Structure-reactivity probes for active site shapes of cholesterol esterase by carbamate inhibitors." BIOCHIMICA ET BIOPHYSICA ACTA, vol. 1431, no. 2, 18 May 1999 (1999-05-18), pages 500-511, XP000964977 ISSN: 0006-3002 page 502; figure 1</p> | 1,43-49, 52 |
| A | <p>RADZICKA, WOLFENDEN: "Transition State and Multisubstrate Inhibitors" METHODS IN ENZYMOLOGY, vol. 249, 1995, pages 284-303, XP000964812 cited in the application page 292, paragraph 3</p> | 1,43-49, 52 |
| P,X | <p>WO 99 60404 A (TRIAD BIOTECHNOLOGY INC ;SEM DANIEL (US)) 25 November 1999 (1999-11-25) page 36, line 3 -page 43, line 25</p> | 1-49,52 |

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| P, A | <p>LIN GIALIH ET AL: "Structure-reactivity relationships for the inhibition mechanism at the second alkyl-chain-binding site of cholesterol esterase and lipase." BIOCHEMISTRY, vol. 38, no. 31, 3 August 1999 (1999-08-03), pages 9971-9981, XP002153170 ISSN: 0006-2960 figure 2</p> <p>-----</p> | 1, 43-49, 52 |

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 50,51,53-58

Present claims 50,51 and 53-58 of the present application (PA) relate to compounds or libraries of compounds defined by reference to a desirable property, namely their ability to bind to a an enzyme having a common ligand (CL) site and a specificity ligand (SL) site.

No technical features of the compounds are present in the above-mentioned claims which would lead to this desirable property, the technical features formulated so as to permit the execution of a meaningful search. No support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found for substances which could fall within the scope of these claims. Suggested pre-selection criteria for members of a library include three-dimensional shape and electronic properties (see e.g. page 39, line 12-17 of the description of the PA), without limitation to any specific chemical functionalities. No definition of the linker in terms of chemical structure, i.e. the number and type(s) of bonds used to connect CL and SL moieties, is provided other than a general indication of how suitable atoms might be identified on CL and SL moieties where a linker could be attached (page 43, line 12 to page 44, line 3, and page 53, lines 10 to 13 of the PA). In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. No means are present in the above-mentioned claims by which compounds known in the prior art could be distinguished from novel substances. No definition of the subject matter for which protection is sought is therefore derivable from these claims (Article 6 PCT) or the description (Article 5 PCT). Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/15310**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 50, 51, 53-58
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Info. on patent family members

Inventor's Application No

PCT, US 00/15310

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| WO 9718469 A | 22-05-1997 | US 5891643 A | 06-04-1999 |
| | | US 5989827 A | 23-11-1999 |
| | | AU 711092 B | 07-10-1999 |
| | | AU 7680496 A | 05-06-1997 |
| | | EP 0870197 A | 14-10-1998 |
| WO 9960404 A | 25-11-1999 | AU 4198699 A | 06-12-1999 |

PATENT COOPERATION TREATY

by fax and post

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

WRITTEN OPINION

(PCT Rule 66)

per Fax am 21.05.01

To:
WEBER-QUITZAU, Martin
UEXKÜLL & STOLBERG
Patentanwälte
Beselerstrasse 4
22007 Hamburg
ALLEMAGNE

21.MAI.2001

040 - 233 - 65488

Date of mailing
(day/month/year) 25.05.2001

Applicant's or agent's file reference
P 56138

REPLY DUE within 1 month(s)
from the above date of mailing

International application No.
PCT/US00/15310

International filing date (day/month/year)
02/06/2000

Priority date (day/month/year)
04/06/1999

International Patent Classification (IPC) or both national classification and IPC
C12Q1/00

Applicant
TRIAD THERAPEUTICS, INC. et al.


1. This written opinion is the first drawn up by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:
 - I ☒ Basis of the opinion
 - II ☒ Priority
 - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☐ Lack of unity of invention
 - V ☒ Reasoned statement under Rule 56.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☒ Certain document cited
 - VII ☒ Certain defects in the international application
 - VIII ☒ Certain observations on the international application
3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 56.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 56.2. For the form and the language of the amendments, see Rules 56.8 and 56.9.

Also: For an additional opportunity to submit amendments, see Rule 56.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 56.4 bis.
For an informal communication with the examiner, see Rule 56.5.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
4. The final date by which the international preliminary examination report must be established according to Rule 59.2 is: 04/10/2001.

Name and mailing address of the international preliminary examining authority:
 European Patent Office
D-80238 Munich
Tel. +49 89 2339 - 0 TX 323656 ppm u
Fax: +49 89 2339 - 4465

Authorized officer / Examiner

Barz, W

Formalities officer (incl. extension of time limits)
Neumann, M
Telephone No. +49 89 2339 7351



WRITTEN OPINION

International application No. PCT/US00/15310

I. Basis of the opinion

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

Description, pages:

1-53 as originally filed

Claims, Nos:

1-58 as originally filed

Drawings, sheets:

1/12-12/12 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

WRITTEN OPINION

International application No. PCT/US00/15310

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This opinion has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 50-51, 53-58,

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings (indicate particular elements below) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):

☒ the claims, or said claims Nos. 44 are so inadequately supported by the description that no meaningful

WRITTEN OPINION

International application No. PCT/US00/15310

opinion could be formed.

☒ no international search report has been established for the said claims Nos. 30-31, 53-58.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Rule 68.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Claims 45-48

Inventive step (IS) Claims

Industrial applicability (IA) Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the International application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**WRITTEN OPINION
SEPARATE SHEET**

International application No. PCT/US00/15310

ITEM III:

1. Concerning claim 44, the present application provides no information on how to achieve the CL/CL mimic exchange (unbinding of Cl and binding of CL mimic) in the presence of the perturbation of a CL atom (steps (2) and (3) of claim 44). Therefore, the subject-matter of claim 44 is neither sufficiently disclosed (Article 5 PCT), nor clear and supported by the description (Article 6 PCT). Consequently, claim 44 cannot be subject of the International Preliminary Examination (Article 34(4)(a)(ii) PCT).
2. Due to lack of disclosure (Article 5 PCT) and/or support (Article 6 PCT), the International Search was not performed for claims 50-51 and 53-58 (see Box 1.2 of the International Search Report). Therefore, said claims will not be subject of the International Preliminary Examination (Rule 66.1(e) PCT).

ITEM II:

The claim to priority does not appear to be valid for claims 16, 19, 24, 28, 31-32, 35, 38-40, and 45-46 of the present PCT application. Therefore, documents which were published after the priority date, but before the filing date of the present application (listed as "P" documents in the International Search Report) belong to the state of the art (Rule 64.1 PCT) for said claims (see item V-1, below).

ITEM V:

Reference is made to the following documents:

- D1: WO 99 60404 A (TRIAD BIOTECHNOLOGY Inc.), 25 November 1999;
D2: SCIENCE, no. 274, 1998, pages 1531-1534, (Shuker S.B. et al.);
ISSN: 0036-8075, cited in the application.

1. NOVELTY

**WRITTEN OPINION
SEPARATE SHEET**

International application No. PCT/US00/15310

Claims 45-46 do not meet the requirements of Article 33(2) PCT for the following reasons:

- 1.1 Methods for identifying atoms of ligands mimics, comprising all features of claims 45-46 are disclosed in document D1 (page 36, line 3 - page 43, line 25). Therefore, the subject-matter of said claims is not novel in the sense of Article 33(2) PCT.
- 1.2 The remaining claims 1-43, 47-49, and 52 appear to be novel, because none of the available prior art documents discloses the same combination of features as in these claims.

2. INVENTIVE STEP

Claims 1-43, 47-49, and 52 appear to involve an inventive step (Article 33(3) PCT) for the following reasons:

- 2.1 Document D2, which is considered to represent the closest prior art, discloses a method termed "SAR by NMR", which identifies ligands and ligands mimics of proteins (abstract; page 1531, left column; page 1532, left column; Fig. 1). Compared to the method of D2, the subject-matter of claim 1 of the present application differs primarily by the facts that an atom of the interface region (step (a)(3) of claim 1) and a proximal atom in the CL mimic (step (b)(3)) are identified. While D2 only identifies ligand molecules that bind to proximal subsites of a protein (e.g. enzyme), present claim 1 relates to the identification of proximal atoms of both the interface region and the CL mimic.

Therefore, the technical problem to be solved by claim 1 may be regarded as how to provide a method for identifying CL mimic atoms proximal to an enzyme's interface region. Since no solution to this problem seems to be disclosed in the available prior art and due to its apparent advantages, claim 1 as well as its dependent claims 2-42 appear to involve an inventive step in the sense of Article 33(3) PCT.

**WRITTEN OPINION
SEPARATE SHEET**

International application No. PCT/US00/15310

- 2.2 Compared to the method of D2, the subject-matter of claim 43 differs by the identification of a proximal atom in the CL mimic (step (3)). Therefore, the technical problem to be solved by claim 43 may also be regarded as how to provide a method for identifying CL mimic atoms proximal to an enzyme's interface region. Again, no solution to this problem seems to be disclosed in the available prior art. Consequently, claim 43 also appears to involve an inventive step (Article 33(3) PCT).
- 2.3 The methods of generating a focused combinatorial library of claims 47-49 also appear to be inventive, because they comprise the inventive method of claim 1.
- 2.4 Finally, the screening method of claim 52 appears to involve an inventive step, because it comprises the inventive method of claim 47.

3. INDUSTRIAL APPLICABILITY

The subject-matter of claims 1-43, 45-49 and 52 appears to be industrially applicable in the sense of Article 33(4) PCT.

ITEM VI:**Certain published documents (Rule 70.10)**

| Application No Patent No | Publication date (day/month/year) | Filing date (day/month/year) | Priority date (valid claim) (day/month/year) |
|-----------------------------|--------------------------------------|---------------------------------|---|
| WO 99 60404 A | 25.11.99 | 21.05.99 | 21.05.98 |

1. The above patent document belongs to the state of the art (Rule 64.1 PCT) for several claims of the present application (see items II. and V-1. above).
2. Furthermore, the above patent document may become relevant prior art for all claims in the Regional phase of the present application.

**WRITTEN OPINION
SEPARATE SHEET**

International application No. PCT/US00/15310

ITEM VII:

1. Contrary to the requirements of Rule 5.1(a)(II) PCT, the relevant background art disclosed in documents D1 is not mentioned in the description, nor is this document identified therein.
2. Since the incorporation of disclosures by reference is not allowed (PCT Guidelines II-4.17), the passage on page 53, lines 14-15, should be deleted.
3. Vague and not precisely defined expressions related to the "spirit" of the invention (page 53, lines 26-29) are unallowable and should be deleted (PCT Guidelines III-4.3a).

ITEM VIII:

1. In claim 1, the definition of the term "interface region" is not clear (Article 8 PCT), because the expression "and atoms of an SL if bound to the enzyme" is not understandable from the wording of the claim alone (PCT Guidelines III-4.2).
2. Similarly, in claims 1 and 18-19, the term "immediately adjacent" does not fulfill the requirements of Article 8 PCT, because it is not understandable from the wording of the claim alone (PCT Guidelines III-4.2).
3. Finally, claim 47 is not clear (Article 6 PCT), because the term "focused" is not understandable from the wording of the claim alone (PCT Guidelines III-4.2).

CONCLUDING REMARKS:

- a) New claims to be filed should take account of all of the above comments.
- b) Amendments should be filed by way of replacement pages.
- c) In the reply, those parts of the application as originally filed which form a basis for the amendment (Article 34(2)(b) PCT, last sentence) should be indicated.